­Sent by email to: XXXXXXXXXXXXXXXXXXX

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The UK Cutaneous Lymphoma Group

25 March 2021

Dear XXXXXXXXX XXXXXXX XXXXX XXX XXXXXXXXX XXXX XXXXXXXXX

**Re: Final Appraisal Document –** **Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]**

Thank you for your letter received on 18 March 2021, lodging the UK Cutaneous Lymphoma Group (UKCLG)’s appeal against the above Final Appraisal Document (FAD).

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to confirm that they are at least arguably within the permitted grounds of appeal ("valid"). The permitted grounds of appeal are:

* 1(a) NICE has failed to act fairly, or
* 1(b) NICE has exceeded powers;
* (2) the recommendation is unreasonable in the light of the evidence submitted to NICE

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information and arguably fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I will make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

I assess each of your points in turn and then summarise the appeal points that I am presently minded to refer at the end of this letter.

You have not allocated your appeal points to a specific appeal ground, but I believe they would all be considered under ground 2. If you disagree please would you make this clear in your reply to this letter.

You make 5 appeal points, as follows.

1. *“The FAD quotes “limitation in trial design” with particular reference to the fact that Vorinostat is not standard treatment in the UK. We recognise that Vorinostat does not have a licence in the UK. We do however strongly feel that Vorinostat is an entirely meaningful comparator in the MAVORIC trial. Standard of care quoted in the FAD refers to Bexarotene, interferon and methotrexate. However, the data assessing the efficacy of these agents is relatively small. The strongest available data relates to the phase II studies published for Bexarotene which demonstrates an ORR of 31 % (Duvic et al 2001). This compares with similar more recent studies published on Vorinostat with similar patient populations demonstrating an ORR of 24%. (Duvic et al 2007) It is also quite clear that although Vorinostat does not have a licence in the UK, the trial data demonstrating its efficacy is more recent and robust in terms of endpoints than historical data for other examples of standard of care such as interferon or methotrexate in this group of patients.”*

I interpret your point to be that the Committee’s treatment of the evidence in which Vorinostat was a comparator led to an unreasonable recommendation. This is a valid appeal point under ground 2.

1. “*We also consider that the decision is inconsistent with previous NICE decisions. Specifically there are examples where drugs have been approved by NICE on the basis of clinical trials where the control arm was not “standard of care” (*[*https://www.nice.org.uk/guidance/ta171/documents/multiple-myeloma-lenalidomide-final-appraisal-determination3*](https://www.nice.org.uk/guidance/ta171/documents/multiple-myeloma-lenalidomide-final-appraisal-determination3) *). It is therefore incorrect for the results of the MAVORIC trial to be disregarded on the basis of an unlicensed control arm when this approach has not been consistently applied for other NICE oncology assessments.*

The substance of this point (i.e. that the Committee’s judgement of the comparator in the MAVORIC trial led to an unreasonable recommendation) is a valid appeal point under ground 2. Given the similarities with your point 1 above, I am minded to refer your points 1 and 2 to be dealt with as a single appeal point.

[For the avoidance of doubt, I do not consider it arguable under ground 1(a) that the Committee was bound as a matter of procedure to adopt the same approach and/or afford the same weight to the MAVORIC evidence (relying on this particular non-standard of care comparator) as that adopted or afforded by other Committees to other trials involving non-standard of care comparators. To guide your preparation for your presentation on this point under ground 2, I would also observe that arguments based on consistency between appraisals will need to establish that the appraisals or their evidence base are sufficiently similar to make consistency a reasonable consideration, and also that committees do have to exercise their own judgement rather than being bound by their predecessors.]

1. *“In the FAD, the panel state that mogamulizumab does not meet the NICE criteria for being considered a life extending treatment at the end of life. We presume that the panel have made this statement because the MAVORIC trial was not designed to demonstrate an overall survival difference between the two treatments. The trial also included a cross-over which further impairs the ability of the trial to show a difference in survival. Firstly, we have grave concerns that NICE appear to be discriminating against cross-over designs. All clinical trials should be designed in the best interest of the participating patient. In the MAVORIC trial, patients were given the opportunity to receive the potential benefit of the trial drug irrespective of the arm they were randomised to. This is clearly in the best interest of the patient and it has a positive impact on the ability to accrue patients to the trial in the intended time interval. These are positive attributes for any clinical trial and should be encouraged and certainly not disincentivised.* *In terms of consistency of NICE decisions, approvals have been made by NICE from trials in which the arms cross over (see below) and so again, approval should not be withheld on the basis of a cross over trial. ”*

I understand this point to be that the Committee’s conclusions in respect of the cross-over trial design rendered its decisions on both the end of life criteria and its recommendation unreasonable.

A valid appeal point under ground 2.

1. *“Prolongation of life is clearly an important aspect in the NICE approval process and the FAD indicates that there was no evidence to suggest that mogamulizumab could prolong life in this group of patients. We strongly disagree with this interpretation. We fully recognise that estimations on impact on survival in this setting are complex. However, we should not let the complexity distract us from identifying a prolongation of life, if in fact it exists. We have studied the data from MAVORIC in detail and have also studied the “Real World” data made available to the panel from the HES database. The HES data demonstrates that in this patient population the median survival is 17.83 months after at least one line of systemic therapy. If we compare this with the outcome for the cohort of patients in MAVORIC who were randomised to receive mogamulizumab, there is a stark difference. When the paper was published (Kim 2018) the analysis was performed after a data lock in December 2016. This constituted a median follow up of 17 months. The data has now been re-analysed with a second data lock in March 2019. This second analysis has occurred 27 months after the initial analysis. On this occasion, the median survival for the patients randomised to receive mogamulizumab is 57.2 months. Clearly this is not a randomised comparison but a difference of this magnitude gives a clear indication of what as clinicians, we are observing directly in our patients who we have treated with mogamulizumab. Specifically, mogamulizumab dramatically changes the course of disease in patients for whom, hitherto, we have had no effective treatment.”*

A valid appeal point under ground 2.

1. *“The most striking aspect for the efficacy of mogamulizumab relates to its mode of action. Throughout the field of oncology, we have recognised that the most aggressive tumours with the worst prognosis respond the least well to any given therapy. Until the appearance of mogamulizumab, this was the case for Sezary syndrome. This is a disease with a documented median survival of 32 months from diagnosis and for which, over the last 30 years, we have had no effective therapy in terms of survival or even disease control. Mogamulizumab targets the circulating malignant lymphocytes resulting in a rapid fall in the number of circulating cells as demonstrated in the MAVORIC study. A recent further analysis of the data from this study has revealed that the highest response rate was seen in patients with the highest number of circulating malignant T-cells (B2 disease). This data is about to be submitted for publication. Until the arrival of mogamulizumab, patients with B2 disease had the shortest survival and the poorest response to current therapies. Every clinician managing patients with Sezary Syndrome recognises that mogamulizumab is dramatic in its efficacy and is transforming the course of the disease in those patients fortunate enough to receive it.”*

I understand this point to be that the FAD is unreasonable because it does not properly take into account the innovative mode of action of mogamulizumab (and resulting benefits to patients).

I am not presently minded to refer this point to the appeal panel, as it is not in my view arguable that the Committee ought to have specifically factored the innovative mode of action of the drug into its assessment of cost effectiveness, given that the clinical benefits arising from the drug (whether owing to its mode of action or otherwise) were captured in the modelling.

As to the aspect of this point relating to “recent further analysis” of the MAVORIC study,I am not persuaded this is a valid appeal point because I do not think the analysis formed part of the evidence base of the appraisal.

In summary, I am presently minded to conclude that there are three valid appeal points all of which are ground 2 appeal points: your points 1 and 2 as a single appeal point, your point 3 and your point 4.

In respect of your point(s) which I am not minded to refer, or that I am minded to amalgamate or refer only under ground 2, you are entitled to submit further clarification and/or evidence to me within the next 10 working days, no later than **Monday 12 April 2021**, and I will then give a final decision on the points to put before an appeal panel. For the points I am already content to refer on, an oral appeal will be held which under current circumstances is likely to be held remotely.

Once I have made my final decision, and where there is more than one appellant, each appellant will receive the valid appeal points of the other appellants and their redacted appeal letter. This is to enable appellants to avoid duplication at the hearing where there are overlapping appeal points. If the appeal letter and/or responses to scrutiny contain confidential information please ensure you have provided a version with this information redacted by **Tuesday 20 April 2021**.

Yours sincerely

Tim Irish

Vice Chair

National Institute for Health and Care Excellence